Direct 3D-printing of cell-laden constructs in microfluidic architectures.

Journal: Lab Chip

Publication Year: 2016

Authors: Justin Liu, Henry H Hwang, Pengrui Wang, Grace Whang, Shaochen Chen

PubMed link: 26980159

Funding Grants: Development of 3D Bioprinting Techniques using Human Embryonic Stem Cells Derived Cardiomyocytes for Cardiac Tissue Engineering

Public Summary:
In the referenced manuscript, we present a new method of constructing a microfluidic lab-on-a-chip (LoC) that allows users to 3D print within. LoC technologies allow for the manipulation of biological fluids and/or mixtures allowing users to measure specific solutions or metabolites, utilizing small volumes and run times. The current gold standard in microfluidic device fabrication is soft lithography, a technique where a 'soft' material like polydimethylsiloxane (PDMS) is used to cast a 3D master molding with micrometer-scale features. Traditional methods for 3D master mold fabrication often require a cleanroom and use standard photolithography methods used in computer chip manufacturing, where multiple high-resolution photomasks must be sequentially-aligned and exposed to build up layers of photoresist into the desired 3D structure. Photolithography tends to be tedious, challenging, and expensive in terms of time, training, and resources, thus limiting final device quality and reproducibility. 3D-printing is emerging as a more preferable method for rapid prototyping of microfluidic device designs and concepts. However, traditional additive manufacturing techniques, such as extrusion-based or inkjet-based 3D-printing suffer from such limitations as poor feature resolution, limited build volumes, and long runtimes. DMD-based printing utilizes an array of millions of individually-controllable micromirrors to project a 2D image onto a prepolymer solution. By projecting light onto the solution, a chemical reaction occurs, hardening the solution in the shape of the image. We utilize an advanced DMD-based technology, micro-continuous optical printing (µCOP) which changes the focal plane while simultaneously changing the image, like a movie. This allows the µCOP system to rapidly produce 3D high-resolution microstructures and grants the ability to rapidly prototype and iterate through master mold generations without the time and resource-intensive issues that plague other 3D-printing techniques. Using the µCOP system, a variable height micromixer (VHM) was designed incorporating rectangular columns of varying heights within zigzagging block shapes that lead to an optically-clear chamber for later fabrication of structures within the chamber. Several architectures were designed and experimentally tested using a dual syringe pump. A solution of fluorescently-labeled sugar and water was flowed in and mixed within the VHM to determine the lowest flow rate to achieve mixing. Unlike other 3D printing technologies, the µCOP system's ability to fabricate structures without physically contacting the printing medium allows users to print a complex 3D scaffold within an already-completed microfluidic device. Using the VHM, a live cell suspension was mixed with a protein-based prepolymer solution called gelatin methacrylate. The mixture was exposed to a complex hexagonal pattern, similar to those found in the liver. We successfully printed a 3D hexagonal scaffold within the VHM microfluidic device. The ability to 3D print cells within complex architectures within microfluidic devices greatly extends our capabilities, with future applications towards human-on-a-chip. This also enables us to better mimic interactions between native tissues and potentially to aid in future drug screening endeavors.

Scientific Abstract:
Microfluidic platforms have greatly benefited the biological and medical fields, however standard practices require a high cost of entry in terms of time and energy. The utilization of three-dimensional (3D) printing technologies has greatly enhanced the ability to iterate and build functional devices with unique functions. However, their inability to fabricate within microfluidic devices greatly increases the cost of producing several different devices to examine different scientific questions. In this work, a variable height micromixer (VHM) is fabricated using projection 3D-printing combined with soft lithography. Theoretical and flow experiments demonstrate that altering the local z-heights of VHM improved mixing at lower flow rates than simple geometries. Mixing of two fluids occurs as low as 320 muL min(-1) in VHM whereas the planar zigzag region requires a flow rate of 2.4 mL min(-1) before full mixing occurred. Following device printing, to further demonstrate the ability of this projection-based method, complex, user-defined cell-laden scaffolds are directly printed inside the VHM. The utilization of this unique ability to produce 3D tissue models within a microfluidic system could offer a unique platform for medical diagnostics and disease modeling.

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